

VASOACTIVE DRUGS IN CRITICAL CARE

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Abstract: This article is a short review of vasoactive drugs which are in use in today's clinical practice. In the past century, development of vasoactive drugs went through several phases. All of these drugs are today divided into several groups, depending on their place of action, pharmacological pathways and/or effects on target organ or organ system. Hence, many different agents are today in clinical practice, we have shown comparison between them. These agents provide new directions in the treatment of cardiovascular compromise, suggesting that the primary goal of therapy is to enhance tissue perfusion by both producing a vasodilatory effect of the circulation and reversing hemodynamic failure using inotropic agents, with increased attention to minimize their inherent risks and side effects.

Key words: vasoactive agents, inotropic agents, levosimendan, phosphodiesterase III inhibitors.

INTRODUCTION

Vasoactive agents are a group of bioactive chemicals, which change vasomotor tone through their influence on various peripheral receptors. Most of these agents have inotropic effects (e.g. norepinephrine) as they bind with receptors positioned on the surface of the myocardium. Some pharmacologic agents are difficult to classify as their effects overlap, however all vasoactive drugs affect stroke volume and heart rate. This determines cardiac output and, as a consequence, overall cardiovascular function. In the ideal situation, inotropic drugs would only have effects directly on myocardial cells, without simultaneous stimulation of other receptors. As one quickly learns, such is not the case with many of our most important vasoactive agents. Some inotropic agents such as dopamine (depending

on the dose) provoke vasoconstriction while other such agents, like isoprenaline, cause vasodilatation.

Pure vasoconstrictors produce arterial wall constriction by stimulation of α -adrenergic receptors (e.g. phenylephrine) or by stimulating V1a receptors (e.g. vasopresine) on the vascular endothelial surfaces.

Pure vasodilators, on the other hand, are classified according to their predominate effect on the arteries (e.g. hydralazine), veins (e.g. nitroglycerine), or both arterial and venous (e.g. nitropruside) vessels. The main favourable result of hydralazine and nitropruside is a reduction of cardiac afterload and an increase in cardiac output. The main effect of nitroglycerine is achieved by venodilatation, which decreases preload and consequently cardiac output.

In 1908, Sir James McKenzie first described "low cardiac output syndrome". Clinically, this syndrome results in global hypo perfusion, whose treatment requires inotropic support by vasoactive medications, or mechanical intervention to support and improve cardiac work. In the early 1900s the mainstay of cardiac treatment was digitalis with the addition of a salt reduced diet. Accumulated fluids within pleural and peritoneal spaces were eliminated by mechanical means or by drainage. The use of diuretics was instituted during the 1920s. The treatment of congestive heart failure entered a second phase in the 1950s, when vasodilators were introduced into the physicians' therapeutic armamentarium. With the introduction of the inotropic agents in the 1980s, a third great period in the therapy of heart failure had begun.

Using the pharmacokinetics and pharmacodynamics of many inotropic agents, Lehtonen was able to categorize them into two basic groups: cAMP dependent (Table 1), and cAMP independent (Table 2) (1).

Table 1. cAMP dependent inotropic agents

INOTROPIC AGENTS
cAMP dependent
adrenergic agonists epinephrine isoproterenol dobutamine xamoterol
dopaminergic agonists dopamine dopexamine ibopamine
phosphodiesterase III isoenzyme inhibitors derivate of biperidine — amrinone, milrinone derivate of imidazolone — enoximone, piroximone toborinone

Table 2. cAMP independent inotropic agents

INOTROPIC AGENTS
cAMP independent
Na ⁺ -K ⁺ -ATPase inhibitors digoxin
potassium channels inhibitors vesnarinone
agonists of α - adrenergic receptors phenylephrine
Calcium

cAMP dependent agents

The cAMP dependent group consists of those agents, which increase production of cAMP by stimu-

Table 3. Older therapeutic medications

OLDER THERAPEUTIC MEDICATIONS
NOTE: treatment of acute heart failure did not change for decades morphine diuretics nitroglycerine catecholamine inotropic agents
Despite acute hemodynamic improvement, inotropic agents often increased mortality epinephrine dobutamine milrinone

Table 4. Adverse effects of catecholamine administration

ADVERSE EFFECTS OF CATECHOLAMINE ADMINISTRATION
increase in oxygen consumption
arrhythmogenic effect
tachyphylaxis
increased risk of sudden cardiac death
difficulty during beta-blocker administration
Dependency on the functional condition of beta-adrenergic receptors

lating adrenergic receptors (adrenergic and dopaminergic agonists) or by decreasing cAMP degradation by inhibiting phosphodiesterase activity (phosphodiesterase III inhibitors). In contrast, the groups of inotropic agents, which are in the cAMP independent group, are inhibitors of Na⁺-K⁺-ATPase (digoxin), potassium

Table 5. Conditions that alter receptor density and affect response to catecholamines

CONDITIONS THAT ALTER RECEPTOR DENSITY AND AFFECT RESPONSE TO CATECHOLAMINES	
CONDITION	RECEPTOR DENSITY CHANGE
congestive heart failure	(heart)*
sepsis	(-) > (liver, vasculature)
myocardial ischemia	(-) beta, (+) > (heart)
asthma	(-) beta (lungs leukocytes)+
cystic fibrosis	(-) beta (leukocytes)
agonist administration	(-) >, beta (heart, platelets, leukocytes)
antagonists administration	(+) >, beta (heart, platelets, leukocytes)
hyperthyroidism	(+) beta (heart)
hypothyroidism	(-) beta (heart)
glucocorticoids	(+) beta (heart, leukocytes)

Legend: *beta — adrenergic receptors are decreased in severe heart failure; + if on beta — agonists therapy for asthma; (+) — increased; (-) — decreased. Modified from: Zaritsky A, Eisenberg MG. Ontogenetic consideration in the pharmacotherapy of shock. In: Chernow B, Shoemaker WC, eds. Critical Care: State of the Art. Fullerton, CA: Society of Critical Care Medicine; 1986;7:485-534

Table 6. Phosphodiesterase III inhibitors

PHOSPHODIESTERASE III INHIBITORS (PDE III)	
NON-SPECIFIC	
theophylline	
papaverine	
dipyridamole	
SPECIFIC	
derivates of biperidine — amrinone, milrinone	
derivates of imidazolone — enoximone, piroximone	

Table 7. Effects of phosphodiesterase III inhibitors

EFFECTS OF PHOSPHODIESTERASE III INHIBITORS	
MYOCARDIUM	positive inotropic
VASCULATURE	vasodilatation
CORONARY ARTERIES	vasodilatation
PLATELETS AND LEUKOCYTES	metabolic effect

channel inhibitors (vesnarinon), agonists of β -adrenergic receptors (phenylephrine), and include the calcium salts. The agents in this latter group affect ionic pumps and regulate the concentration of intracellular calcium (Table 3).

The catecholamine inotropic agents were among the earliest vasoactive agents and remain important and useful today although there can be some negative consequences of their use (Table 4). A major side effect is an increase in myocardial oxygen consumption. Furthermore, it is well established that during dopamine administration its effectiveness diminishes significantly as administration continues beyond 48 hours. This same effect has been seen after 90 hours with dobutamine. The most important component to explain the decreased effectiveness of inotropic agents is the functional condition of the β -adrenergic receptors. Today, there are many known conditions which change the density and responsiveness of β -adrenergic receptors. Such conditions, in fact, change the relationship within subgroups of β -adrenergic receptors in myocardium, from 80% β_1 : 20% β_2 changing in 60% β_1 : 40% β_2 (Table 5) (2).

Table 8. Advantages of phosphodiesterase III inhibitors

ADVANTAGES OF PHOSPHODIESTERASE III INHIBITORS
myocardial — positive lusitropic effect
independent of the functional condition of adrenergic receptors
lack of tachyphylaxis
lack of tachycardia

Phosphodiesterase III inhibitors produce their effects independently of β -adrenergic receptors. They are a useful class of agents that can be employed in various therapeutic settings. They are a non-specific heterogeneous group of agents. All three phosphodiesterase fractions are physiologically active. They have strong chronotropic effects, and therefore should be avoided in clinical practice when an inotropic agent is needed. Specific inhibitors of this class of agents are divided into the two groups (Table 6) (2).

cAMP independent agents

There is also a group of vasoactive agents that exhibit an inotropic effect, but in addition, also have a vasodilator effect. Opie grouped these agents into a unique class, the inodilators (Table 7) (3).

A lack of tachyphylaxis and tachycardia, and being independent of β -adrenergic receptor conditions, gives a clinical advantage to this group of agents, when comparing them with the catecholamines (Table 8).

Furthermore, these agents have a very important myocardial effect, called the lusitropic effect, which was introduced into clinical terminology by Smith and Katz in 1986. Coining this term, the authors wanted to emphasize the role of diastolic dysfunction (4) during heart failure. All agents, which improve diastolic function, primarily by decreasing the actin-myosin overlap during diastole, are deemed to have a positive lusitropic effect. Numerous adverse effects and an increased mortality are the reasons why many clinicians are often unsuccessful with the inotropic agents presently in use. New therapeutic agents have been developed in the last few

Table 9. New therapeutic goals

NEW THERAPEUTIC GOALS		
AGENT	EFFECT	MECHANISM OF ACTION
ISDN - high doses	venous and arterial vasodilatation	synthesis of NO
Tezosentan	arterial vasodilatation	blockade of endothelin receptors
Nesiritide	arterial vasodilatation	decrease of preload, afterload, diuresis
Levosimendan	inotropic, vasodilatation	binding for troponin C, activation of potassium channels

years to assist the clinician in the stabilization, support and treatment of cardiovascular disease (Table 9).

One of the newest groups of inotropic agents (Table 10) is a group of agents, which increase the affinity of myofibrils for calcium and are called calcium sensitizers. Calcium sensitizers are the newest heterogeneous group of inotropic agents. The best known representatives of this group are levosimendan and pimobendan. Positive inotropic effects of levosimendan are achieved by its binding to troponin C and calcium, thereby stabilizing the tropomyosin molecule and prolonging the duration of actin-myosin overlap without a change in the net concentration of intracellular calcium. The vasodilatory effect of levosimendan is reached through activation of ATP-dependent potassium channels. This leads to a decrease in both afterload and preload, increased coronary blood flow and a resultant anti-ischemic effect. Levosimendan is therefore categorized as an anti-ischemic inotropic agent (5). Additionally, the incidence of arrhythmias is extremely low, there is no development of tolerance to its pharmacological effects, and the simultaneous administration of β -blockers and calcium channels blockers does not produce serious adverse effects.

In two large randomized studies, RUSSLAN and LIDO, it was documented that positive hemodynamic effects and a lower mortality was seen in patients who received levosimendan in comparison to patients who received dobutamine or placebo (6, 7). Also, there is much interest in levosimendan administration in patients with open-heart surgery, especially in those with off-pump procedure (8–10, 11, 12). A recent meta-analysis has shown that levosimendan reduces mortality and duration of hospital stay in patients who underwent cardiac surgery as well as in those who were treated in cardiology units (13).

There are three types of natriuretic brain peptides. The A and B types are located in the atria and ventricles of the heart, and the C type is located in endothelial cells. B-natriuretic peptide has a spectrum of physiologic effects of clinical importance, which include reduction of both pre- and afterload along with diuretic and

Table 10. *Newer inotropic agents*

NEWER INOTROPIC AGENTS
CALCIUM SENSITIZERS levosimendan pimobendan
OTHERS natriuretic brain peptide — nesiritide tezosentan vasopressin

natriuretic effects (Table 11). The serum level of B-natriuretic peptide is directly correlated with the degree of chronic heart failure. Because of this, it has been added to the diagnostic protocol of the European Cardiology Association and to the protocol of congestive heart failure treatment as well (14).

Nesiritide is an exogenous recombinant B-natriuretic peptide with the same pharmacological profile. There have been nine clinical studies conducted using nesiritide involving over nine hundred patients. Significant, positive clinical effects have been documented.

Endothelin is a strong vasoconstrictor. There are two types of receptors to which it attaches. The ET_A receptors are located in the vessel's smooth muscles cells and the ET_B receptors are located on the endothelial surfaces. Stimulation of the receptors by endothelin produces increased vascular tonus and progression of arteriosclerosis in subjects with coronary artery disease. Inhibition of endothelin function results in better hemodynamics, heart remodeling and a decreased proliferation of smooth muscles in blood vessel walls. In the RITZ study, and the VERITAS study, involving almost 1500 patients (15), favorable hemodynamic effects (a lowering the systemic blood pressure, and increase of cardiac index) were measured but without significant clinical improvement and or a reduction in mortality (4, 5, 16).

Arginin-vasopressine is an endogenous nonapeptide. It stimulates V1a receptors and produces vasoconstriction. At the same time stimulation of V2 receptors produces an antidiuretic effect. By these mechanisms vasopressine plays an important role in fluid homeosta-

Table 11. *B-type natriuretic peptide (bnp) – physiologic effects*

B-TYPE NATRIURETIC PEPTIDE (BNP) — PHYSIOLOGIC EFFECTS	
Systemic Hemodynamic preload reduction afterload reduction increased CI lack of tachycardia	Neurohormonal decrease endothelin 1 inhibit RAA axis decrease of epinephrine level
Coronary arteries vasodilatation	Renal diuresis and natriuresis increased filtration fraction GFR effect variable

sis. It plays an important therapeutic role in states of refractory vasodilatation, in which patients are unresponsive to catecholamine vasoconstrictive therapy (17). Vasopresine has also a place in cardiopulmonary resuscitation procedures (18). In the animal model, it has shown better effects on circulation in the splanchnic region in comparison with norepinephrine (19).

CONCLUSION

Historically, the catecholamines inotropic agents were first line medications used in the treatment of cardiovascular compromise, but their benefits were often overshadowed by major complications, such as increased mortality. The introduction of many newer agents in newer classes, such as those which produce their effects independently of b-receptor functionality (e.g. phosphodiesterase III inhibitors), or do not change the intracellu-

lar calcium values (e.g. calcium sensitizers), represent safer, better choices for treatment. They also establish new directions in the treatment of cardiovascular compromise, suggesting that the primary goal of therapy is to enhance tissue perfusion by both producing a vasodilatory effect of the circulation and reversing hemodynamic failure using inotropic agents, with increased attention to minimize their inherent risks and side effects.

Abbreviations

cAMP — cyclic adenosine monophosphate
ATP — adenosine triphosphate
ISDN — isosorbiddinitrate
NO — nitric oxide
CI — cardiac index
RAA — renin-angiotensin-aldosterone system
GFR —glomerular filtration rate

Sažetak

VAZOAKTIVNI LEKOVI U INTENZIVNOJ MEDICINI

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Ovaj rad je kratki pregled vazoaktivnih lekova koji su u primeni u današnjoj kliničkoj praksi. Tokom poslednjeg veka, razvoj vazoaktivnih lekova prošao je kroz nekoliko faza. Svi ti lekovi danas su podeljeni u nekoliko grupa, u zavisnosti od njihovog mesta delovanja, farmakoloških puteva i/ili učinaka na ciljani organ ili organski sistem. Stoga je danas mnogo različitih lekova u kliničkoj praksi, a u ovom radu prikazujemo poređenja među nji-

ma. Navedeni lekovi pružaju nam nove smerove u lečenju kardiovaskularno kompromitovanih bolesnika, uz poboljšanje tkivne perfuzije ostvareno vazodilatatornim svojstvima i reverzijom srčanog zatajenja korištenjem inotropnih lekova, sa povećanom pažnjom usmerenom prema smanjenju rizika i nuspojama njihovog korišćenja.

Ključne reči: vazoaktivni lekovi, inotropni lekovi, levosimendan, inhibitori fosfodiesteraze tipa III.

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